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NONPRESCRIPTION DRUG MANUFACTURERS ASSOCIATION



*Better Health Through Responsible Self-Medication*

January 4, 1994

William E. Gilbertson, Pharm.D.
Director
Monograph Review Staff
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
7520 Standish Place
Rockville, MD 20855

Re: Docket No. 78N-0065

Dear Dr. Gilbertson:

On behalf of the NDMA Hydroquinone Task Group, I am submitting scientific and market research information to update FDA on research activities undertaken by the task group in response to various issues associated with hydroquinone as an OTC skin lightening agent.

The Nonprescription Drug Manufacturers Association (NDMA) is a 112 year-old trade organization representing the manufacturers and distributors of nonprescription medicines and nutritional supplements. By sales, NDMA members represent over 95% of the OTC marketplace, and in the case of OTC hydroquinone-containing products task group members market all the major brands.

The following materials are appended to this letter:

A An Update on Chronic Health Effects Testing for Hydroquinone

B Ochronosis Recall Survey

The data developed for this update support the conclusions that: (a.) hydroquinone in OTC skin lightening preparations does not present a carcinogenic risk when used according to label directions; and (b.) ochronosis is a rarely reported event and there are no scientific data to specifically point to currently marketed OTC hydroquinone-containing preparations as causes of exogenous ochronosis.

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## A. An Update on Chronic Health Effects Testing for Hydroquinone

In May, 1992 NDMA outlined to FDA a research plan to provide additional information to more completely understand the significance of previous animal test results. At that time NDMA defined a hypothesis based on the available scientific data that the benign kidney neoplasms seen in male Fischer 344 rats are due to an unusual sensitivity of this animal model to hydroquinone.

The results of some of the studies incorporated in the 1992 plan are presented in the appended follow-up report (Appendix A) which also includes preliminary information for on-going studies and an outline of studies that are in the planning phase. The results of the completed and on-going research continue to support the conclusion reached in the 1992 plan and submitted to FDA.

In short, the appended research results demonstrate that the male Fischer rat develops a toxic nephropathy which is unusual in that: (a.) male Sprague-Dawley rats given similar doses of hydroquinone do not demonstrate a similar toxic effect; and (b.) female Fischer rats, while susceptible to developing nephropathy, are not as susceptible as male Fisher rats and do not develop benign renal neoplasms after long term hydroquinone exposure.

The nephropathy that is seen in the male Fischer rat is associated with an increase in the rate of renal epithelial cell proliferation but is not associated with the formation of DNA adducts in the target cell population. At dose levels that are nephrotoxic, hydroquinone binding to renal cellular proteins can be observed. In this nephropathy, protein binding may play a role in the pathogenesis of renal damage as Sprague-Dawley rats show less protein binding than male Fischer 344 rats when dosed orally but show much higher levels of protein binding when they are dosed by a route of administration (ip) that overwhelms their normal defense mechanisms and induces nephropathy.

Of more direct importance to the risk assessment process are data that demonstrate that hydroquinone is only slowly absorbed through rat and human skin. The dermal toxicity and cell proliferation study with Fischer 344 rats which is underway will provide important information about whether or not dermal hydroquinone exposure can be associated with renal effects in this sensitive model of nephropathy.

In summary, the data collected in this research program support the conclusion made in the 1992 NDMA report to FDA that hydroquinone in nonprescription skin lightening preparations does not present a human carcinogenic risk when used according to label directions.

**B. Ochronosis Recall Survey:**

The Ochronosis Recall Survey was suggested by FDA in order to compile non-documented reports of cases of ochronosis and antecedent exposure to skin-lightening agents over the life-time medical practices of members of the American Academy of Dermatology (AAD).

Over a lifetime medical practice base of over 44 million patients reportedly estimated by 2,108 AAD physicians (i.e., 32% of AAD members), 46 cases were reportedly associated with 2% hydroquinone and "OTC bleaching creams;" 215 cases were reportedly associated with Rx or unspecified types of hydroquinone products and the remaining 216 cases with sources other than hydroquinone. Whether the 14 domestic published cases of ochronosis that were reported to FDA by NDMA in May, 1992 are part of these reported cases -- and they may be -- is unknown.

Of note is the remark by Market Measures Inc. on the limitations of the survey data: "This study is unique and distinctly different from other market surveys conducted by Market Measures Inc. in that each physician was asked to report recall and frequency of a rare condition over the entire lifetime of his/her practice. In all other surveys based on recall conducted by Market Measures Inc. over the 25 years that Market Measures Inc. has been active in survey research, the longest previous recall period has been one year."

Market Measures Inc. continues with several other caveats concerning the limitations of the survey findings, particularly as they might be misrepresented as population incidence data. Specifically, Market Measures Inc. states: "Additionally, hydroquinone manufacturers and distributors that are members of NDMA and represent about 70% of the hydroquinone marketplace initiated significant labeling changes in May, 1992. This consumer labeling emphasizes discrete usage of OTC hydroquinone products (see Appendix A of Report, which is Appendix B to this letter). No attempt was made to distinguish consumer v. patient usage of OTC and Rx product or use prior to and after the initiation of labeling changes, since (a.) no attempt was made to obtain the available medical records (i.e., to confirm exposure); and (b.) the [new] OTC label has not been on OTC hydroquinone products for a sufficiently long period to affect the survey results. . . No attempt was made to create an 'incidence figure' for ochronosis by this survey. This is because of the nature of the recall (i.e., over full length of medical practice spanning many years), lack of confirmation of diagnosis, lack of confirmation of reported drug exposure either by medical records or patient interview, no determination of coincident cases among reporting physicians. etc."

In summary, the NDMA Hydroquinone Task Group continues to conclude that ochronosis is a rare disorder and that there are no scientific data that specifically implicate currently labeled OTC hydroquinone products as causes of exogenous ochronosis.

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**C. Conclusion and request for a Feedback Meeting:**

In conclusion, the on-going research program continues to support the safety of OTC hydroquinone-containing skin lighteners for OTC use according to label directions.

In view of the fact that some time has elapsed since our last meeting on this subject, I have been asked by the Hydroquinone task group to request a feedback meeting with FDA in order to review the on-going research program. At the time of the meeting we anticipate to have additional scientific data which were completed only in preliminary form prior to the 1993 year end holidays and not in final form for inclusion herein. I look forward to your response on this request.

Sincerely yours,

R. William Soller, Ph.D.

R. William Soller, Ph.D.
Senior Vice President and
Director of Science & Technology

cc: Dockets Management Branch (Original and 3 Copies)

Appendices A An Update on Chronic Health Effects Testing for Hydroquinone

B Ochronosis Recall Survey

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